REMARKS

Claims 3 and 9-26 were previously withdrawn from further consideration and claims 28-32 were previously cancelled.

Claims 1, 2, 4-8, and 27 are under examination. Applicants respectfully request that the Examiner reconsider this application in view of the following remarks.

Rejection under 35 U.S.C. § 103

Claims 1, 2, 4-8, and 27 are rejected for obviousness on two grounds, each of which is traversed below.

I

The Examiner rejects claims 1, 2, and 5-8 for obviousness relying on Hwang et al., US Patent 5,905,089 (Hwang) and Baba et al., US Patent 6,123,943 (Baba). Independent claims 1 and 5 will be discussed first.

Claim 1 covers treating hepatitis C virus (HCV) infection with a sesquiterpene lactone compound. Claim 5 covers treating HCV infection with a sesquiterpene lactone compound featuring γ-lactone fused with a 10-membered ring.

Hwang describes a group of sesquiterpene lactone compounds that inhibit NF-κB activity. Nowhere is it taught or even suggested in this reference treating HCV infection with these compounds.

Baba describes that 1,2,3,4-tetrahydroisoquinoline compounds can be used to treat a large number of diseases (including viral hepatitis) by inhibiting NF-κB activity. It does not teach or suggest any sesquiterpene lactone compound, let alone using it to treat any viral hepatitis, not to mention HCV infection.

In response to the last office action, Applicants pointed out that, to come up with the claimed HCV infection treatment, one skilled in the art would have had to first select HCV infection from a very large number of diseases described in Baba, then replace the 1,2,3,4-tetrahydroisoquinoline compounds described in Baba with the sesquiterpene lactone compounds described in Hwang, and, finally, use them to treat HCV infection. Applicants further stated that, given the large size of the number of diseases described in

Baba and unpredictable nature of the pertinent art, he or she would not have been motivated to arrive at the claimed treatment. Of note, according to MPEP 2144.08.II.4,[1] to determine whether there is motivation to select a species from a prior art genus, the Examiner must consider factors including the size of the genus and the predictability of the technology.

In the final Office Action, the Examiner asserts that "the list of diseases [mentioned in Baba] is not very large since one of ordinary skill in the art could have readily envisioned [treating HCV infection] with a reasonable expectation of success." See page 6, lines 5-7.

Applicants do not agree. Baba states that:

> The present invention also relates [] to a method [] particularly for the treatment and prevention of inflammatory diseases, for the treatment and prevention of autoimmune diseases and for the treatment and prevention of viral diseases. Column 3, lines 5-15.

Clearly, according to Baba, any inflammatory disease, any autoimmune disease, and any viral disease can be treated with 1,2,3,4-tetrahydroisoquinoline compounds via inhibiting NF-κB activity. There are a vast number of different inflammatory diseases, a vast number of different autoimmune diseases, and a vast number of different viral diseases encompasses. Thus, contrary to the Examiner's belief, the number of the diseases mentioned in Baba is extremely large. Of note, Baba provides a relatively smaller list of diseases to be treated by 1,2,3,4-tetrahydroisoquinoline compounds. The number of diseases in this list is still very large. Applicants have reproduced this list below:

> That is, the drug of the present invention is effective for the treatment and prevention of diseases such as rheumatoid arthritis, systemic lupus erythematosus, systemic scleroderma, Behcet

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[1] It states that "[t]o address this key issue [i.e., whether it would have been obvious to select the claimed species from the disclosed prior art genus], Office personnel should consider all relevant prior art teachings, focusing on the following, where present... (a) Consider the Size of the Genus ... (e) Consider the Predictability of the Technology ..."

> disease, periarteritis, ulcerative colitis, Crohn disease, active chronic hepatitis, glomerular nephritis and the like various autoimmune diseases; and osteoarthritis, gout, atherosclerosis, psoriasis, atopic dermatitis, pulmonary diseases with granuloma, various intractable diseases in which inflammatory symptoms such as of various types of encephalitis are the basis of the morbid state, endotoxin shock, sepsis, inflammatory colitis, diabetes, acute myelocytic leukemia, pneumonia, heart transplantation, encephalomylitis, anorexia, acute hepatitis, chronic hepatitis, drug induced hepatic injury, alcoholic hepatitis, viral hepatitis, jaundice, hepatic cirrhosis, hepatic insufficiency, atrial myxoma, Castleman syndrome, multiple myeloma, Rennert T lymphomatosis, mesangial nephritis, renal cell carcinoma, cytomegaloviral hepatitis, cytomegaloviral retinopathy, adenoviral cold syndrome, adenoviral pharyngoconjunctival fever, adenoviral ophthalmia, AIDS and the like. Column 8, lines 26-46.

The list includes many encompassing terms, e.g., various intractable diseases, viral hepatitis (including, among others, HCV and HBV), and diabetes (including Type I diabetes and Type II diabetes). In short, even this smaller list encompasses a large number of diseases. Thus, contrary to the Examiner's assertion, the genus disclosed in Baba is very large.

Further, Applicants would like to point out that, contrary to the Examiner's belief, one of ordinary skill in the art would not "have readily envisioned [treating HCV infection] with a reasonable expectation of success." As discussed above, according to Baba, any inflammatory disease, any autoimmune disease, and any viral disease can be treated by an NF-κB inhibitor. As a patent, Baba understandably asserts treatment of as many diseases as possible, even though treatment of most of the receited diseases is clearly inoperable. One of ordinary skill would have recognized that such an omnipotent drug does not, and cannot, exist. Indeed, given the high unpredictability of the medicine field, he or she would have expected that **the same NF-κB inhibitor has different efficacies in treating different NF-κB related diseases**. Baba provides data that only show inhibition of NF-κB activity and HIV-1 LTR transcription activity by a 1,2,3,4-tetrahydroisoquinoline compound. One of ordinary skill, in view of this data, would have predicted with a reasonable expectation of success only that 1,2,3,4-

tetrahydroisoquinoline compounds can be used to treat HIV infection by inhibiting NF-κB activity. On the other hand, absent additional data, he or she would not have been able to predict with a reasonable expectation of success that 1,2,3,4-tetrahydroisoquinoline compounds can be used to treat other diseases, let alone HCV infection, by inhibiting NF-κB activity.

Regardless, one skilled in the art would have predicted with an even lower expectation of success that the sesquiterpene lactone compounds described in Hwang can be used, in place of the 1,2,3,4-tetrahydroisoquinoline compounds described in Baba, to treat HCV infection. Note that Hwang does not provide any evidence that sesquiterpene lactone compounds actually had any therapeutic utility. As already pointed out in the last response, **different NF-κB inhibitors may have totally different effects in treating the same disease**. To support this statement, Applicants submitted with the last response a copy of Aubin et al., J. Neurochem., 1998, 71:1635-1642 ("Aubin"), which discloses that, while aspirin, a well-known NF-κB inhibitor, inhibits MPTP-induced dopamine depletion in mice, dexamethasone, a much more potent NF-κB inhibitor, is totally ineffective against MPTP toxicity in this dopamine depletion mouse model. Turning to the instant case, whether or not 1,2,3,4-tetrahydroisoquinoline compounds could be effectively used to treat HCV infection, one could not have predicted with any expectation of success that sesquiterpene lactone compounds, the NF-κB inhibitors described in Hwang, can be used in place of 1,2,3,4-tetrahydroisoquinoline compounds, the NF-κB inhibitors described in Baba, to treat HCV infection.

To further support the above conclusion, Applicants would like to submit herewith as "Exhibit A" a declaration by Professor Sui-Yuan Chang at National Taiwan University, who specializes in therapy of infectious diseases, e.g., HIV, herpes, and viral hepatitis. In the declaration, Professor Chang describes two assays she and her colleagues conducted to test parthenolide, a sesquiterpene lactone compound, on its efficacy in treating cytomegalovirus (CMV) infection disclosed in Baba. The results show that this compound showed cytopathic effect in CMV-infective culture and did not repress CMV production, indicating that it is not effective in treating CMV infection.

Thus, even though Baba suggests treating CMV hepatitis via inhibiting NF-κB activity, parthenolide, an NF-κB inhibitor, is not active in this treatment. In other words, as stated by Professor Chang in the declaration, one skilled in the art, in view of Hwang and Baba, would not have expected that the sesquiterpene lactone compounds disclosed in Hwang can be used to treat viral hepatitis disclosed in Baba, including HCV infection, given the unpredictability of the medicine field.

Of note, the Examiner asserts in the final Office Action that "[a] patent shall be presumed valid." See page 6, line 17. Referring to 35 U.S.C. § 282, he further asserts that "[e]ach claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims." See page 6, lines 17-20. It appears to be the Examiner's position that, whether the pertinent art is unpredictable or not, mere description of the subject matter in the prior art is sufficient to establish prima facie obviousness. Applicants disagree on two grounds.

First, the Examiner incorrectly relies on 35 U.S.C. § 282. This provision is categorized in Chapter 29 entitled "Remedies for Infringement of Patent and Other Actions." It clearly concerns infringement of a patent. That is, in infringement matters, claims of an issued patent are presumed to have legal force.[2] It has nothing to do with veracity of the disclosure in the patent. Indeed, since only claims have been examined before a patent is issued, the disclosure in the patent, usually broader than the claimed subject matter that is finally allowed, may not have been verified. Thus, it is improper to presume the veracity of the disclosure of a patent. To this end, Applicants would like to point out that (1) Baba, as an issued patent, only includes claims covering methods of inhibiting NF-κB activity, not treating any disease, and (2) treatment of diseases, which is relied on by the Examiner, is mentioned in the specification, but not recited in any claim of Baba.

Second, "**mere ... description** of the subject matter [in a prior art reference] is **insufficient,** if it cannot be produced without undue experimentation." MPEP § 2121.01,

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[2] According to the online dictionary http://www.merriam-webster.com/dictionary/, the word "valid" means "having legal efficacy or force."

emphases added. Here, Baba merely describes treating various diseases. As the pertinent art is highly unpredictable, one skilled in the art would not be able to practice the treatment without undue experimentation. Thus, contrary to the Examiner's belief, mere description of treating viral hepatitis in Baba, not even HCV infection covered by claims 1 and 5, would not be sufficient to constitute prior art against these two claims.

In sum, the size of the genus of diseases mentioned in Baba is very large and any utility relating to inhibition ofNF-κB is highly unpredictable. In view of these facts, Applicants submit that one skilled in the art, in view of Hwang and Baba, would not have been motivated to treat HCV infection with sesquiterpene lactone compounds to arrive at the methods covered by claims 1 and 5. In other words, claims 1 and 5 are not rendered obvious by these two references.

For the same reasons set forth above, claim 2, dependent from claim 1, and claims 6-8, dependent from claim 5, are also not rendered obvious by these two references.

II

The Examiner rejects claims 4 and 27 for obviousness, relying on Hwang, Baba, and Tan et al., Nature Review, 2002, 1: 867-881 (Tan).

Claims 4 and 27 depend from claims 1 and 5, respectively. Their patentability resides at lease in part in treating HCV infection with a sesquiterpene lactone compound. As discussed above, Hwang and Baba, taken alone or in combination, do not teach or suggest such treatment. Tan also fails to do so. It merely discloses treating HCV infection using intron A, which is a protein, not a sesquiterpene lacton compound.

As none of Hwang, Baba, and Tan teaches or suggests treating HCV infection with a sesquiterpene lacton, any combination of these three references also fails to do so. As such, claims 4 and 27 are not rendered obvious by these three references.

CONCLUSION

It is believed that all of the pending claims have been addressed. However, the absence of a reply to a specific rejection, issue or comment does not signify agreement

with or concession of that rejection, issue or comment. In addition, because the arguments made above may not be exhaustive, there may be reasons for patentability of any or all pending claims (or other claims) that have not been expressed. Finally, nothing in this paper should be construed as an intent to concede any issue with regard to any claim, except as specifically stated in this paper, and the amendment of any claim does not necessarily signify concession of unpatentability of the claim prior to its amendment.

Please apply any charges to Deposit Account No. 50-4189, referencing Attorney Docket No. 70001-021001.

Respectfully submitted,

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Y. Rocky Tsao, Ph.D., J.D.
Attorney for Applicants
Reg. No. 34,053

Customer No. 69713
Occhiuti Rohlicek & Tsao LLP
10 Fawcett Street
Cambridge, MA 02138
Telephone: (617) 500-2503